CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Jan. 2002, p. 182–183 Vol. 9, No. 1
1071-412X/02/$04.00+0 DOI: 10.1128/CDLI.9.1.182–183.2002

NOTES

Feed a Cold, Starve a Fever?

Gijs R. van den Brink,* Daniëlle E. M. van den Boogaardt, Sander J. H. van Deventer, and Maikel P. Peppelenbosch

Laboratory for Experimental Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands

Received 20 June 2001/Returned for modification 5 September 2001/Accepted 21 September 2001

An English old wives' tale advises us to "feed a cold and starve a fever." Here we report that the nutritional status modulates the T helper 1 (Th1)-Th2 balance of activated T cells in human volunteers. Food intake resulted in increased levels of gamma interferon production, whereas food deprivation stimulated interleukin-4 release.

Even though popular wisdom holds that one should "feed a cold and starve a fever," it is, to the best of our knowledge, not known if nutrient availability acutely modulates the immune response. The adaptive immune response uses different strategies to ward off infection by pathogens. A subset of T lymphocytes, the CD4-expressing T helper (Th) cells, are important in directing this strategy (3). So-called Th1 cells primarily stimulate the cell-mediated immune response against intracellular invaders by activating macrophages and $CD8^+$ cytotoxic T lymphocytes (1, 4). Th2 cells favor the B-cell-dependent humoral immune response against extracellular organisms (2, 5). Whereas gamma interferon (IFN-γ) is the hallmark Th1 cytokine (1, 4), interleukin-4 (IL-4) is an important Th2 cytokine (2, 5). We decided to study the Th1-Th2 balance in the blood of healthy volunteers in response to food intake.

Six nonsmoking healthy male volunteers (mean age, 28 years; age range, 26 to 33 years; mean body mass index, 23.8; body mass index range, 21.5 to 26.3) were studied on two occasions. The medical ethical committee of our hospital approved the study. After overnight starvation the participants received a liquid meal on one occasion (800 ml of Nutridrink [Nutricia, Zoetermeer, The Netherlands], which contains 1,200 kcal, 40 g of protein, 144 g of carbohydrate, and 88 g of lipids) and an equal volume of water on the second occasion. The water was used to control for gastric distension. Heparinized blood was obtained at the start of the experiment at 9:00 a.m. and every hour for 6 h thereafter. Blood was diluted 1:1 in pyrogen-free medium (RPMI 1640; Bio Whittaker, Verviers, Belgium), and 1-ml aliquots were cultured in triplicate for 24 h in the presence or absence of the T-cell-receptor-activating antibodies anti-(α)-CD3 and anti-α-CD28 (concentrations, 1.5 and 2 μg/ml, respectively; CLB, Amsterdam, The Netherlands). IFN-γ and IL-4 levels were measured by enzyme-linked immunosorbent assay (assay kits were from CLB) according to the manufacturer's protocol. All time points for a volunteer were measured in the same assay.

The levels of both IFN-γ and IL-4 in unstimulated blood were below the detection limit of the assay. Upon stimulation for 24 h, the mean baseline levels (at time zero) of IL-4 production were 61 ± 22 pg/ml for controls and 62 ± 43 pg/ml for volunteers about to receive Nutridrink. Baseline levels of IFN-γ were 76 ± 55 and 85 ± 38 ng/ml in the two groups, respectively. Thus, the baseline cytokine levels were comparable in both groups. These levels were altered in blood obtained at later time points both in the calorie-fed group and in the control group. Six hours after calorie ingestion, six of six volunteers showed strongly increased levels of IFN-γ production, averaging 450% of the baseline value (range, 117 to 867%). Fasting, however, decreased the levels of IFN-γ production to an average of 83% of the baseline value (range, 47 to 115%) (Fig. 1). Both calorie intake and water ingestion increased the levels of IL-4 production. The increases were significantly higher, however, in fasted volunteers, with the most marked difference being noted 5 h after intake of a meal. Whereas in the fasted controls the level of IL-4 production reached an average of 398% of the baseline value (range, 67 to 1114%), after food intake the level of IL-4 production reached only an average of 142% of the baseline value (range, 80 to 243%) (Fig. 1). Hence, food intake acutely increases the IFN-γ response but not the IL-4 response of T lymphocytes. Conversely, starvation increases the IL-4 response but not the IFN-γ response of T lymphocytes.

Calorie ingestion apparently favors cell-mediated immunity (as evidenced by the dramatic upregulation of IFN-γ production) (1, 4), whereas starvation skews the immune system toward a humoral immune response (2, 5). In our approach with whole blood, we did not correct for possible changes in white blood cell counts; it is possible that these are influenced by food intake. We believe, however, that this is unlikely to have an effect on the Th1/Th2 ratio observed in our study, and such differences would be unlikely to explain our results. Although further studies are clearly needed for a better comprehension of the relation between food consumption and the immune

* Corresponding author. Mailing address: Laboratory for Experimental Internal Medicine, Room G2-130, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Phone: 31-20-5668781. Fax: 31-20-6977192. E-mail: g.r.vandenbrink@amc.uva.nl.

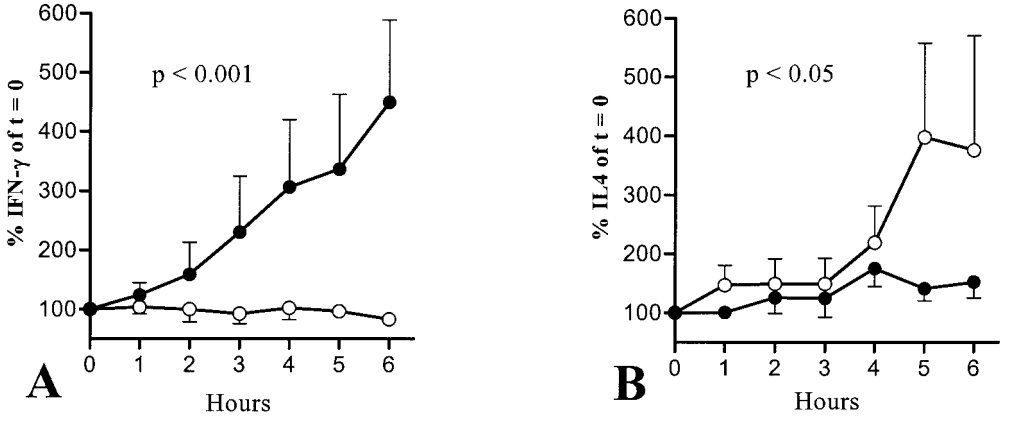

FIG. 1. Changes in levels of IFN-γ (A) and IL-4 (B) production in response to intake of a meal ($n = 6$; closed circles) and fasting ($n = 6$; open circles) during a 6-h follow-up. The data represent the percent cytokine production relative to that at the baseline. Baseline levels (at time zero) of IL-4 production were 61 ± 22 pg/ml in controls and 62 ± 43 pg/ml in volunteers about to receive Nutridrink. Baseline levels of IFN-γ production were 76 ± 55 and 85 ± 38 ng/ml in the two groups, respectively. Statistical analysis was performed by using a two-factor repeated-measurement design with absolute measurements relative to the baseline level (6). The food-time interaction was significant for both cytokines ($P < 0.001$ for IFN-γ; $P < 0.05$ for IL-4).

response, our data support the notion that such a relation does exist. Our results also have the important implication that one should carefully standardize food intake when comparing the levels of cytokine production between different time points or different people. Thus, the English popular belief "feed a cold, starve a fever" may reflect the observation that the nutritional status has a bona fide effect on the regulation of the immune response.

REFERENCES

1. **Cher, D., and T. Mosmann.** 1987. Two types of murine helper T cell clone. II. Delayed type hypersensitivity is mediated by Th1 clones. J. Immunol. **138:** 3688–3694.
2. **Coffman, R. L., B. W. P. Seymour, D. A. Lebman, D. D. Hiraki, J. A. Christiansen, B. Shrader, H. M. Cherwinski, H. F. J. Savelkoul, F. D. Finkelman, M. W. Bond, and T. R. Mosmann** 1988. The role of helper T cell products in mouse B cell differentiation and isotype regulation. Immunol. Rev. **102:**5–28.
3. **Glimcher, L. H., and K. M. Murphy.** 2000. Lineage commitment in the immune system: the T helper lymphocyte grows up. Genes Dev. **14:**1693–1711.
4. **Guidotti, L. G., and F. V. Chisari.** 2001. Noncytolytic control of viral infections by the innate and adaptive immune response. Annu. Rev. Immunol. **19:**65–91.
5. **Killar, L., G. MacDonald, J. West, A. Woods, and K. Bottomly.** 1987. Cloned Ia restricted T cells that do not produce IL4/BSF-1 fail to help antigen specific B cells. J. Immunol. **138:**1674–1679.
6. **Snedecor, G. W., and W. G. Cochran.** 1967. Statistical methods. The Iowa State University Press, Ames.